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Specialty Conference

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The Obese Diabetic

A Symposium on New Developments

Genetics of Diabetes Mellitus

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DIABETES MELLITUS is a major public health problem that affects approximately 2 percent of the American population. Although an enormous amount of research has been done on this disease in the past 50 years, its pathogenesis is still largely unknown. Hereditary factors are generally accepted to be of great etiologic importance, but there is little agreement as to the nature of the genetic mechanisms involved.[1-3]

Evidence in favor of a large genetic component is based primarily on studies of the familial aggregation of the disease, studies of twins and studies of population, using markers such as clinical diabetes, abnormalities in glucose tolerance tests, the secretion of insulin and thickening of the basement membrane.[1,4-12] Regardless of the marker used, be it clinical diabetes or abnormal glucose tolerance, there is a significantly greater prevalence of abnormality among the relatives of diabetic persons than among similar relatives of those who do not have the disease. In almost none of these studies, however, were individual family units examined, nor was there any attempt to define different genetic forms of diabetes. Although the evidence derived from studies of familial ag-

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gregation and twins leaves no doubt as to the etiologic importance of genetic factors in diabetes, the mode of inheritance of the diabetic trait(s) is unknown.[1,2]

During the past several decades every possible mode of genetic transmission has been proposed, and objections have been raised to all of them. This disagreement is due in part to a number of obstacles with which the geneticist is confronted in his attempts to unravel this problem. These include vast differences in the definition of an affected person or an affected relative. For example, to meet the criteria in some studies an affected person must have significant clinical symptoms of the disease, while in others only a mildly abnormal glucose tolerance test is accepted. The clinical variability, variability in the age of onset of the disease, and susceptibility to environmental factors present further difficulties to the delineation of an affected person. Furthermore, the high prevalence of the disease in the population raises questions of relative genetic fitness. The most important impediment to genetic analysis, however, is the lack of knowledge concerning the basic defect in diabetes. Because of this, there is no certain method for detecting prediabetic persons—that is, those with the mutant genotype who have, as yet, no signs of carbohydrate intolerance.

Although the mode of transmission of the diabetic genotype is obviously in question, many investigators have accepted the autosomal recessive hypothesis as fact and have based their definition of "prediabetics" on this assumption. If such were the case, all offspring of two diabetics must possess the diabetic genotype. However, only about 50 percent of such offspring have been found to be affected, irrespective of the marker used to define diabetes.[13-16] These observations may be the result of several factors. First, there may be incomplete penetrance of the gene. Second, diabetes may not be inherited as a simple, autosomal recessive trait, but rather as a dominant or polygenic trait. Multiple factors are certainly involved in the variability of normal blood sugar levels but polygenic inheritance as a cause of clinical diabetes mellitus has not been proven. Indeed, recent studies by Steinberg et al[17] have demonstrated bimodality in blood sugar concentrations in populations with a high prevalence of the disease. Third, diabetes mellitus may be a heterogeneous group of disorders—that is, a number of distinct disorders caused by different gene mutations at different loci, each of which results in carbohydrate intolerance.[1,2]

TABLE 1.—*Genetic Syndromes Associated with Glucose Intolerance*

Alstrom syndrome
Ataxia telangiectasia
Cockayne syndrome
Cystic fibrosis
Friedreich's ataxia
Glucose-6-phosphate dehydrogenase deficiency
Type I glycogen storage disease
Hemochromatosis
Huntington's chorea
Hyperlipemia, diabetes, hypogonadism, and short stature
Hyperlipoproteinemia III
Hyperlipoproteinemia IV
Hyperlipoproteinemia V
Isolated growth hormone deficiency
Laurence-Moon-Biedl syndrome
Lipoatrophic diabetes
Muscular dystrophy
Myotonic dystrophy
Ocular hypertension induced by dexamethasone
Optic atrophy and diabetes
Optic atrophy, diabetes insipidus, and diabetes mellitus
Hereditary relapsing pancreatitis
Photomyoclonus, diabetes, deafness, nephropathy, and cerebral dysfunction
Pineal hyperplasia and diabetes
Acute intermittent porphyria
Pheochromocytoma
Prader-Willi syndrome
Retinitis pigmentosa, neuropathy, ataxia and diabetes
Schmidt syndrome
Werner syndrome
Turner syndrome
Klinefelter syndrome
Down syndrome

TABLE 2.—*Risk of Development of Diabetes When a Parent, Sibling or Child Is a Diabetic*

Age of Nondiabetic (years)	*Risk of Diabetes (percent)*
0 - 19	< 1
20 - 39	1
40 - 59	3
60 +	10

(After Simpson, NE[5])

Evidence in favor of the hypothesis of heterogeneity includes (a) clinical variability in the disease, as exemplified by the differences between juvenile and maturity onset diabetes, (b) ethnic variability in the clinical and metabolic features of diabetes apparently not directly related to environmental factors, (c) biochemical heterogeneity as exemplified by both insulinopenic and hyperinsulinemic forms of diabetes, and (d) the occurrence of abnormal glucose tolerance in over 30 distinct genetic syndromes due to mutations at many different loci, as well as to several chromosomal aberrations[1] (Table 1). Furthermore,

TABLE 3.—*Genetically Transmitted Syndromes with Obesity*

	Rodent	*Man*
Dominant	Yellow Mouse	Achondroplasias
Recessive	Obese Mouse Fatty Rat Diabetes Mouse* Adipose Mouse*	Laurence-Moon-Biedl
Polygenic	Japanese KK Mouse New Zealand Obese	

*Allelomorphic.

genetic heterogeneity has been well documented in mice, being associated with at least four simply inherited disorders due to mutations at different loci, as well as being present in high frequency in a number of distinct strains which have been developed by selection and inbreeding (Table 3). All of this evidence points toward the possibility that diabetes represents a heterogeneous group of disorders and that hyperglycemia is a non-specific manifestation of a variety of different mechanisms. Indeed, hyperglycemia may be no more specific than anemia, and the use of diet, oral hypoglycemic agents or insulin may be as non-specific as a blood transfusion.

Theoretically, there are a number of ways in which the mutation of a gene could affect insulin synthesis, secretion, transport or action so as to produce carbohydrate intolerance. Some of these possibilities include a structural mutation in the insulin molecule, a defect in the enzyme which cleaves insulin from proinsulin, decreased synthesis or secretion of a normal insulin molecule, glandular hypoplasia or degeneration, peripheral unresponsiveness to the actions of insulin, or circulating antagonists to insulin action. It is likely that many, if not all, of these mechanisms do produce abnormal glucose tolerance, and future research into this symptom-complex must provide a means of identifying the specific pathogenetic mechanism operating in each diabetic patient before accurate genetic counselling can be given.

Since the mode of inheritance of diabetes is still in question, accurate genetic counselling is impossible. Various tables listing the risk of an individual's inheriting the diabetic genotype have been published, based on the assumption that diabetes is inherited as a simple autosomal recessive trait[20] or on the basis of a statistical analysis of morbid risk figures, calculated from limited clinical experience.[21] Simpson[3,21] has constructed relative risk figures for the development of clinical diabetes among first degree relatives of diabetics, based on data obtained from questionnaires on a large population (Table 2). The risk of a given relative's developing diabetes varies with the age at onset of diabetes in the proband. If diabetes developed in the proband at less than 20 years of age, the risk figures should be approximately doubled, except for persons over 60 years of age. If there is more than one parent, sibling or child who is diabetic, the risks are also approximately doubled. These relative risk figures are, of course, approximations and must be related to the age-specific risk for diabetes in the specific population from which the person being counselled derives. Although these risk figures allow the counselor the satisfaction of quoting a number to the person he is counselling, the inexactness should be made clear.

There has recently been some controversy on whether or not diabetics should be allowed to marry one another and have children. The World Health Organization[22] advises that they should be counselled not to marry each other, or that if they do they should not have children. The WHO bases this advice on the presumption that "conjugal diabetics may increase the number of diabetic offspring and perhaps determine the appearance of diabetics at earlier ages." Edwards[23] pointed out the fallacy of this advice and claimed that these recommendations would probably not increase the number of subsequent diabetics but would simply influence their allocation. It is apparent that, with our limited knowledge concerning the genetics of diabetes, it is difficult to offer informative genetic counselling to an individual couple, and foolhardy to attempt eugenic measures.

Obesity

Genetic factors also play a role in the transmission of certain forms of obesity.[19] Among experimental animals, distinct forms of hereditary obesity have been described with different modes on inheritance (Table 3). The yellow obese mutation of mice is transmitted as a dominant trait. In the yellow pure form, homozygosity for the mutation is lethal (A^y), but among two alleles in a mottled yellow coat color, obesity can be present (A^{iy}; A^{vy}) without being lethal. In four distinct disorders of rodents, obesity is inherited as an autosomal recessive trait.

The most widely known example of this group is the obese mouse, ob/ob (synonym, obese-hy-

perglycemic mouse). Although the obesity is not present at birth, the animal becomes corpulent within the first three or four weeks of life and continues to gain weight thereafter, reaching a body weight which can be more than three times that of its siblings. "Adipose" is a second mutation in the mouse resulting in recessively inherited obesity. Matings between carriers of the gene for adipose and carriers of the gene for obese do not produce fat offspring, indicating that these two genes (ob and ad) are not allele. A third mouse, "diabetes" (db), is also fat, but in addition suffers from diabetes. Twenty-five percent of the offspring from matings between carriers of ad and db genes are obese, indicating that these two mutants are allele. The fatty rat is another mutation in the rodent in which obesity is transmitted as an autosomal recessive trait. Polygenic inheritance of obesity has also been described in two inbred strains of mice called New Zealand Obese and the Japanese KK mouse. The variety of rodents with genetically transmitted obesity suggests that obesity is a heterogeneous trait in man.[23]

That genetic factors also pay a prominent role in the development of human obesity is shown in the results of twin studies and in studies of families of obese and lean persons.[24] In one study, a number of anthropological measurements were made on 57 pairs of twins. Weight had the widest variability among these measurements, but was usually within a small difference even when the environmental background had been dissimilar. Thus, environmental factors play a greater role in determining body weight than in determining the length of the arm, overall height, or such dimensions as the circumference of the head or neck. Comparison of identical and fraternal twins has shown much more variability among the fraternal twins and siblings than between the pairs of identical twins. Indeed, only 2 percent of the identical twins differed in weight by more than 12 pounds in contrast to 25 percent of the dizygotic twins. The importance of genetic factors is also apparent in examining the offspring of various types of marriages. When two "lean" persons marry, only rarely are the offspring obese. The offspring of the overweight population tended to be overweight but with a greater variability than was observed among the offspring of lean marriages.[25] Although such findings could be ascribed to environmental differences, they are likely due in part to differences in genotype upon which any environmental factors operate.[26]

Control of Insulin Secretion

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INSULIN OCCUPIES the central role in the modulation of the body's fuel metabolism.[27] The introduction of the radioimmunoassay procedure[28,29] permitted extensive investigations of the factors controlling endogenous insulin secretion. However, because secreted insulin first enters the portal circulation and is extracted by the liver to a variable extent, peripheral plasma levels cannot be equated with secretion. To delineate more precisely the relationship between stimulus and response, a number of approaches, including pancreatic perfusion, pancreatic slices or isolated pancreatic islets, have been utilized. This review aims to be a synthesis of known facts primarily as they pertain to humans. Other reviews have recently appeared.[30,31] Throughout, the term *insulin concentration* refers to levels measured by radioimmunoassay. It should be remembered that immunoreactivity cannot be equated with biological activity. For example, the biosynthesis of insulin, a dipeptide molecule linked by disulphide bridges, involves a third connecting peptide chain. This precursor, proinsulin, will be measured as insulin in most immunoassay procedures, although it is structurally distinct, and biologically less active.[32]

Fortunately, except in patients with insulinoma, proinsulin accounts for only some 10 to 20 percent of measurable immunoreactive insulin, and hence alterations in insulin levels following physiological manipulation *in vivo* or *in vitro* do not in probability reflect insulin secretion.

Basal Insulin

Although the beta cell of the pancreas is capable of responding to a stimulus, it also maintains a basal level of insulin secretion. In a human, following an overnight fast, insulin levels do not fall to zero, but are maintained within a defined normal range, declining even further in parallel with glucose during a prolonged fast.[33] Glucose thus appears to be involved in the direct feedback mechanisms for basal insulin levels. However,

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